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Risk of cardiovascular events and death associated with initiation of SGLT2 inhibitors compared with DPP-4 inhibitors: an analysis from the CVD-REAL 2 multinational cohort study

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Summary

Background Cardiovascular outcome trials have shown cardiovascular benefit with sodium-glucose co-transporter-2 (SGLT2) inhibitors in patients with type 2 diabetes, whereas dipeptidyl peptidase-4 (DPP-4) inhibitors have not shown an effect. We aimed to address knowledge gaps regarding the comparative effectiveness of SGLT2 inhibitor use in clinical practice (with DPP-4 inhibitor use as an active comparator) across a range of cardiovascular risks and in diverse geographical settings.

Methods In this comparative cohort study, we used data from clinical practice from 13 countries in the Asia-Pacific, Middle East, European, and North American regions to assess the risk of cardiovascular events and death in adult patients with type 2 diabetes newly initiated on SGLT2 inhibitors compared with those newly initiated on DPP-4 inhibitors. De-identified health records were used to select patients who were initiated on these drug classes between Dec 1, 2012, and May 1, 2016, with follow-up until Dec 31, 2014, to Nov 30, 2017 (full range; dates varied by country). Non-parsimonious propensity scores for SGLT2 inhibitor initiation were developed for each country and patients who were initiated on an SGLT2 inhibitor were matched with those who were initiated on a DPP-4 inhibitor in a 1:1 ratio. Outcomes assessed were hospitalisation for heart failure, all-cause death, myocardial infarction, and stroke. Hazard ratios (HRs) were estimated by country and then pooled in a weighted meta-analysis.

Findings Following propensity score matching, 193 124 new users of SGLT2 inhibitors and 193 124 new users of DPP-4 inhibitors were included in the study population. Participants had a mean age of 58 years (SD 12·2), 170 335 (44·1%) of 386 248 were women, and 111 933 (30·1%) of 372 262 had established cardiovascular disease. Initiation of an SGLT2 inhibitor versus a DPP-4 inhibitor was associated with substantially lower risks of hospitalisation for heart failure (HR 0·69, 95% CI 0·61–0·77; p<0·0001), all-cause death (0·59, 0·52–0·67; p<0·0001), and the composite of hospitalisation for heart failure or all-cause death (0·64, 0·57–0·72; p<0·0001). Risks of myocardial infarction (HR 0·88, 0·80–0·98; p=0·020) and stroke (0·85 0·77–0·93; p=0·0004) were significantly but modestly lower with SGLT2 inhibitors versus DPP-4 inhibitors.

Interpretation In this large, international, observational study, initiation of SGLT2 inhibitors versus DPP-4 inhibitors was associated with lower risks of heart failure, death, myocardial infarction, and stroke, providing further support for the cardiovascular benefits associated with use of SGLT2 inhibitors in patients with type 2 diabetes.

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Introduction

Type 2 diabetes confers a two-to-three-times increased risk of cardiovascular events, and cardiovascular mortality is the leading cause of death in patients with type 2 diabetes. As well as cardiovascular events such as myocardial infarction, stroke, and cardiovascular death, patients with diabetes are also at an increased risk of heart failure and those patients who develop heart failure are at a significantly increased risk of death.[1]

Sodium-glucose co-transporter-2 (SGLT2) inhibitors are glucose-lowering drugs widely used in the treatment of type 2 diabetes. Cardiovascular outcome trials showed that SGLT2 inhibitors, added on top of existing therapy, significantly reduced the risk of major adverse cardiovascular events in patients with type 2 diabetes and atherosclerotic cardiovascular disease or chronic kidney disease,[2,3] and the risk of hospitalisation for heart failure in patients with type 2 diabetes both with and without established atherosclerotic cardiovascular disease.[2,4–6] On the basis of these results, the European Association for the Study of Diabetes and American Diabetes Association[1] recommend that patients with type 2 diabetes and

Research in context

Evidence before this study

Sodium-glucose co-transporter-2 (SGLT2) inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors are modern glucose-lowering drugs widely used in the treatment of type 2 diabetes. We searched PubMed for publications in English from Jan 1, 1990, to Feb 14, 2020, which reported findings from studies that compared the cardiovascular outcomes of treatment with SGLT2 inhibitors versus DPP-4 inhibitors, using the search terms "SGLT-2", "SGLT-2 inhibitor", "DPP-4", "DPP-4 inhibitor", "cardiovascular", "CV", "diabetes", "T2D", and "T2DM". No head-to-head cardiovascular outcome trials were identified. A network meta-analysis of placebo-controlled studies indirectly compared different glucose-lowering treatments and showed a reduced risk of death with SGLT2 inhibitors compared with DPP-4 inhibitors. An observational analysis of data from three countries assessed a single SGLT2 inhibitor (dapagliflozin) and showed that, compared with DPP-4 inhibitors, treatment was associated with lower risks of major adverse cardiovascular events, hospitalisation for heart failure, and death in more than 40 000 patients with type 2 diabetes. Another analysis of data from two commercial and one federal claims data sources in the USA showed that initiation of an SGLT2 inhibitor (empagliflozin), versus a DPP-4 inhibitor (sitagliptin), decreased the risk of hospitalisation for heart failure in more than 32 000 patients with type 2 diabetes. A Scandinavian registry cohort study of cardiovascular outcomes with SGLT2 inhibitors and DPP-4 inhibitors showed a reduced risk of heart failure with SGLT2 inhibitors, but no reduction in major cardiovascular events. We did an additional search of PubMed (Jan 1, 1990, to Feb 14, 2020) for randomised controlled trials in English comparing SGLT2 inhibitors and DPP-4 inhibitors, using the MeSH terms "Sodium-Glucose Transporter 2 Inhibitors" and "Dipeptidyl-Peptidase IV Inhibitors" and the publication type "Randomized Controlled Trial". One study, VERTIS FACTORIAL, was identified as the only non-pharmacokinetic randomised trial with direct comparison of SGLT2 inhibitors and DPP-4 inhibitors. In this study, coadministration of ertugliflozin and sitagliptin provided more effective glycaemic control up to 52 weeks than either drug alone, but clinical endpoints were not reported.

Added value of this study

This large, population-based, international, observational study directly comparing SGLT2 inhibitors with DPP-4 inhibitors included more than 386 000 matched patients from more than 2·4 million patients with type 2 diabetes from 13 countries across four global regions. It included the largest number of cardiovascular events of all observational studies of SGLT2 inhibitors to date, over a median follow-up of 1·2 years. To our knowledge, this is the first study to compare SGLT2 inhibitors with DPP-4 inhibitors for a broad range of cardiovascular outcomes, including hospitalisation for heart failure, death, stroke, and myocardial infarction, using routine clinical practice data from nearly all major global regions. Our findings showed that initiation of an SGLT2 inhibitor was associated with a significantly lower risk for all of these outcomes compared with initiation of a DPP-4 inhibitor. These findings complement those of randomised clinical trials, which did not include head-to-head comparisons of SGLT2 inhibitors and DPP-4 inhibitors.

Implications of all the available evidence

SGLT2 inhibitors and DPP-4 inhibitors are widely used in everyday clinical practice, and health-care practitioners and patients should be aware of the comparative effectiveness of these two drug classes, including with respect to cardiovascular outcomes associated with the use of these agents. As there are no clinical trials that directly compare SGLT2 inhibitors with DPP-4 inhibitors in terms of their cardiovascular effects, our data provide the most comprehensive assessment to date. Our analysis shows that initiation of an SGLT2 inhibitor rather than a DPP-4 inhibitor was associated with substantially lower risks of heart failure and death and modestly lower risks of myocardial infarction and stroke in clinical practice. The two drug classes both reduce HbA_{1c} to a similar extent (although this effect is not completely equivocal and can differ with patients' kidney function) and are associated with low risk of hypoglycaemia and weight gain, suggesting that the cardiovascular effects of SGLT2 inhibitors could be independent of these mechanisms. These findings are especially important, because, as seen in our study, a much larger proportion of patients were initiated on DPP-4 inhibitors than SGLT-2 inhibitors across most geographical regions. Our findings provide further support for the cardiovascular benefits associated with use of SGLT2 inhibitors in patients with type 2 diabetes.

established atherosclerotic cardiovascular disease receive an SGLT2 inhibitor or a glucagon-like peptide-1 (GLP-1) receptor agonist, with an SGLT2 inhibitor preferred in patients at high risk of heart failure or with coexisting heart failure, as well as in those with chronic kidney disease. However, complementary data that includes patients from various geographical locations and across a broad spectrum of cardiovascular risk are needed.

For the present study, we chose dipeptidyl peptidase-4 (DPP-4) inhibitors as the active comparator because, like SGLT2 inhibitors, these are a modern class of drugs that are frequently used as second-line therapy in type 2 diabetes management. To date, DPP-4 inhibitors have shown no effect on ischaemic events or cardiovascular death, and, for the most widely used DPP-4 inhibitor (sitagliptin), no effect on hospitalisation for heart failure, making them an ideal comparator for pharmacoepidemiological studies intended to assess cardiovascular outcomes associated with glucose-lowering drugs.[6–10] No cardiovascular outcome trial has incorporated head-to-head

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See Online for appendix

comparisons of SGLT2 inhibitors and DPP-4 inhibitors; network meta-analyses providing comparative information suggest that SGLT2 inhibitors are associated with lower all-cause and cardiovascular mortality than DPP-4 inhibitors,[11] although low event rates limited the assessment of effects in patients at low risk. Previous analyses of real-world data (including CVD-REAL) have compared initiation of an SGLT2 inhibitor with initiation of any other glucose-lowering drug.[12,13] However, the effect of glucose-lowering drugs on cardiovascular outcomes can vary, and therefore, analysis with DPP-4 inhibitors (thought to be neutral with respect to cardiovascular outcomes) as the comparator was considered a useful approach. Use of SGLT2 inhibitors has been compared with use of DPP-4 inhibitors in large-scale administrative datasets.[14,15] In the EMPRISE study, which used commercial and federal databases in the USA, the use of an SGLT2 inhibitor, empagliflozin, was associated with a decreased risk for hospitalisation for heart failure compared with the DPP-4 inhibitor sitagliptin, but other cardiovascular outcomes have not yet been examined.[14] In a study of new users of SGLT2 inhibitors or DPP-4 inhibitors from Scandinavian registries, SGLT2 inhibitors were associated with a lower risk of heart failure compared with DPP-4 inhibitors, but not the composite of major cardiovascular events.[15] However, several important questions remain. First, the applicability of findings to patients worldwide, particularly to those residing outside of the USA and Europe, remains unclear. Second, it is unknown whether the observed benefits associated with SGLT2 inhibitors are limited to the outcome of heart failure alone given the existing evidence.

To complement large cardiovascular outcome trials and address the knowledge gaps regarding the comparative effectiveness of SGLT2 inhibitors across a broad range of cardiovascular risk and in diverse geographical settings, we used data from routine clinical practice across 13 countries in the Asia-Pacific, Middle East, European, and North American regions. We aimed to compare the risk of hospitalisation for heart failure, death, the composite of hospitalisation for heart failure or death, myocardial infarction, and stroke between patients newly initiated on SGLT2 inhibitors or DPP-4 inhibitors.

Methods

Data sources and study population

In this comparative cohort analysis from the CVD-REAL 2 study, de-identified health records from 13 countries (Australia, Canada, Denmark, Germany, Israel, Japan, Norway, Singapore, South Korea, Spain, Sweden, Taiwan, and the USA) were analysed. Descriptions of the data sources can be found in the appendix (pp 2–3).

Patients with type 2 diabetes were identified with standard diagnosis codes (appendix pp 4–11). All incident (first) episodes of new initiation of either SGLT2 inhibitors or DPP-4 inhibitors were selected, if the date of first prescription or pharmacy dispensation was within the country-specific date range (start date range of Dec 1, 2012, in Denmark to May 1, 2016, in Taiwan; appendix p 12). New users were defined as patients written or dispensed a prescription (as initial or add-on therapy) for any SGLT2 inhibitor (canagliflozin, dapagliflozin, and empagliflozin [all countries apart from South Korea]; ipragliflozin [South Korea and Japan]; and tofogliflozin and luseogliflozin [Japan only]) or DPP-4 inhibitor (including fixed-dose combinations; sitagliptin and saxagliptin [all countries]; linagliptin [all countries apart from Germany]; vildagliptin [all countries apart from the USA and Canada]; alogliptin [South Korea, Japan, Australia, USA, and Spain]; anagliptin and tenegliptin [South Korea and Japan]; gemigliptin and evogliptin [South Korea only]; and trelagliptin and omarigliptin [Japan only]), without any use of either drug during the preceding 12 months.

Additional inclusion criteria were patients aged 18 years or older on the index date (defined as the prescription date for new initiation of an SGLT2 inhibitor or DPP-4 inhibitor), and more than 1 year of data history in the database before the index date. Patients with type 1 or gestational diabetes were excluded. Patients were followed up from the index date until the end of the index treatment, migration or leaving the practice or database, last date of data collection, outcome date, or censoring date (range of Dec 31, 2014, in Australia to Nov 30, 2017, in Singapore; appendix p 12).

Analyses of de-identified patient record data were done in accordance with local laws and regulations and received approvals from respective scientific, ethics, or data protection committees in all participating countries. Because of the de-identified nature of patient records, informed consent was not required.

Outcomes

Outcomes assessed were hospitalisation for heart failure, all-cause death, the composite of these two outcomes (ie, death or hospitalisation for heart failure), non-fatal myocardial infarction, and non-fatal stroke. Data for deaths were available for all countries. Data for the other outcomes were available for all countries apart from Australia. Outcomes were defined on the basis of primary discharge diagnosis codes (appendix p 12). For Japan and Singapore, only information about in-hospital deaths were available; however, in-hospital deaths represent the majority of fatal events in these countries according to national statistics.[16,17] For Denmark, Norway, and Sweden, hospitalisation for heart failure was defined by any hospital visit, including outpatient visits, with a registered main diagnosis of heart failure (defined from diagnosis codes [appendix p 12], and validated independently in each country).

Statistical analysis

To avoid immortal time bias, only the first incident episode during the inclusion period of either SGLT2 inhibitor or a DPP-4 inhibitor treatment was eligible for inclusion.[18] A requirement for entry as a new user in our cohort was that

individuals were free of both SGLT2 inhibitors and DPP-4 inhibitors during a 1-year washout period before entry. This so-called new-user design avoids a situation in which patients initially given one drug class (eg, a DPP-4 inhibitor) and then switched to the comparator class (eg, an SGLT2 inhibitor) could be assigned to the SGLT2 inhibitor group, or vice versa, which could create immortal time bias. Patients initiated on an SGLT2 inhibitor and a DPP-4 inhibitor on the same date were also excluded.

A non-parsimonious propensity score for initiating an SGLT2 inhibitor was developed (separately within each country) for each individual episode of new treatment initiation. Variables that could potentially affect treatment assignment or outcomes were selected (appendix pp 13–14; baseline comorbidity information not available for Australia, although extensive medication data were available). On the basis of propensity scores, patients initiating an SGLT2 inhibitor were matched 1:1 with patients initiating a DPP-4 inhibitor. The adequacy of matching was assessed by post-match standardised differences in patient characteristics. A non-negligible imbalance was considered if a more than 10% standardised difference occurred between the two groups after matching.

Baseline characteristics are reported as descriptive statistics. Categorical variables are described by frequencies and percentages, and continuous variables reported as means and SDs. For continuous variables, the overall mean across all databases was a summary estimate of country-specific means, weighted according to the number of patients in each country. The proportion of exposure time contributed by individual agents is summarised both overall and by country.

The incidence rate of each outcome was assessed by treatment group. Only the first occurrence of each outcome was included, and the crude incidence rate calculated as the number of events divided by the total number of person-years at risk. The time to first event was compared between groups with Cox proportional-hazards models, presented as hazard ratios (HRs) and 95% CIs for each outcome separately by country. The primary analysis used an intention-to-treat (ITT) approach in which patients were followed-up from the start of index treatment until either occurrence of the first outcome event, or the censoring date (whichever came first), irrespective of whether index treatment was discontinued.

The HRs for each endpoint from each individual country were then pooled for an overall weighted summary,[19] with the use of random-effects models with inverse variance weighting for each country.[20] Analyses for all outcomes were then stratified according to the presence or absence of previous known cardiovascular disease (with the relevant diagnosis codes for cardiovascular disease [myocardial infarction, coronary artery bypass graft, percutaneous coronary intervention with stent, unstable angina, angina pectoris, heart failure, atrial fibrillation, stroke, transitory ischaemic attack, and peripheral artery disease]), to examine whether the effectiveness differed across these subgroups. Subgroup analyses of patients with and without established cardiovascular disease were adjusted for several covariates: age, sex, frailty, hypertension (if available), obesity or BMI (if available), duration of diabetes (if available), and use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), β blockers, calcium-channel blockers, statins, loop diuretics, and thiazide diuretics. Analyses were also repeated with an on-treatment approach in which follow-up was censored at index treatment discontinuation. Additionally, to test the robustness of our data, an analysis that removed the data from one country at a time was done.

Country-specific analyses were done by independent academic or statistical groups. Aggregated results from each country were entered into an Excel file and managed separately by a commercial firm (Statisticon, Uppsala, Sweden). All participating analytical groups used the same study protocol and statistical analysis plan to harmonise the data analyses. Quality checks on the data output from each country were done by a statistical expert (MT) and several members of the study scientific committee. Meta-analyses were done by Statisticon and validated by independent academic statisticians at Saint Luke's Mid America Heart Institute (Kansas City, MI, USA).

For the pooled analyses, R version 3.5.0 was used. The significance level was 5%, but as no adjustment for multiplicity was done, all p-values should be interpreted accordingly.

Role of the funding source

The funder of the study was involved in study design, data collection, data analysis, and data interpretation. Employees of the funder were authors on this paper, and were therefore involved in writing of the report. Editorial support in styling, formatting, and submitting this report was provided by a medical writer funded by the sponsor. The corresponding author and senior author had full access to all the data in the study, vouch for the accuracy

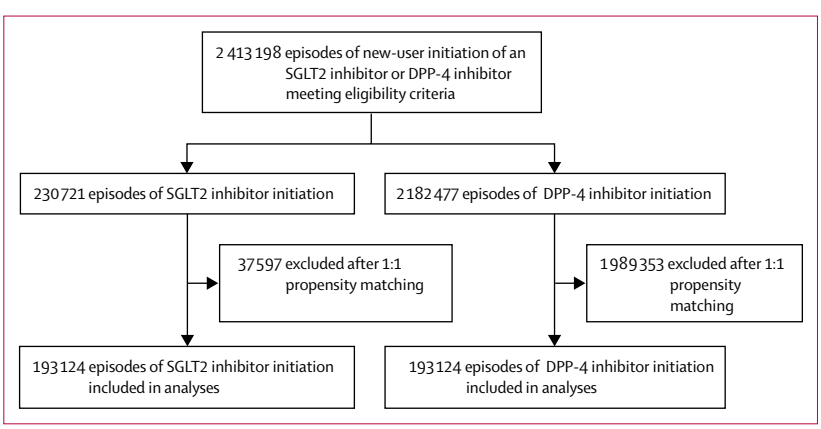


Figure 1: **Study profile for all countries combined**
SGLT2=sodium-glucose co-transporter-2. DPP-4=dipeptidyl peptidase-4.

and completeness of data reported, and had final responsibility for the decision to submit for publication.

Results

2 413 198 patients who were newly initiated on either an SGLT2 inhibitor or a DPP-4 inhibitor were identified, of whom 230 721 (9·6%) were new users of SGLT2 inhibitors and 2 182 477 (90·4%) were new users of DPP-4 inhibitors (figure 1). Initiation of a DPP-4 inhibitor was more common than initiation of SGLT2 inhibitors across the four geographical regions (appendix p 15). Before propensity matching, patients initiated on SGLT2 inhibitors were younger and had slightly lower rates of stroke at baseline, but higher rates of peripheral artery disease. Use of statins, ACE inhibitors, and low-ceiling diuretics (eg, thiazides) was higher, and use of loop diuretics and ARBs was lower in patients initiated on SGLT2 inhibitors versus those initiated on DPP-4 inhibitors. Patients initiated on SGLT2 inhibitors were also more likely to be receiving other types of glucose-lowering drugs at baseline before matching, including metformin, GLP-1 receptor agonists, and insulin (appendix p 16).

Following propensity matching, there were 193 124 new users of SGLT2 inhibitors and 193 124 new users of DPP-4 inhibitors remaining; 16% of new users of SGLT2 inhibitors were excluded because of having no appropriate match (figure 1). Baseline characteristics were well balanced between groups post-matching (table), with standardised differences for all variables less than 4%. Overall, mean age was 58 years (SD 12·2), 170 335 (44·1%) of 386 248 were women, and 111 933 (30·1%) of 372 262 had established cardiovascular disease. Overall, 241 112 (62·4%) of 386 248 patients received statins, 265 332 (68·7%) received antihypertensive drugs, 91 270 (23·6%) received ACE inhibitors, 147 509 (38·2%) received ARBs, and 303 801 (78·7%) received metformin.

The distribution of specific SGLT2 inhibitor drugs initiated and the distribution of specific DPP-4 inhibitor drugs are shown in the appendix (pp 17). Dapagliflozin contributed 60% of total exposure time in the SGLT2 inhibitors class, followed by canagliflozin (23%), and empagliflozin (13%), with other SGLT2 inhibitors providing minimum contributions (all <3%; appendix p 17). Sitagliptin contributed 49% of total exposure time in the DPP-4 inhibitors class, followed by linagliptin (20%), and saxagliptin (11%), with other DPP-4 inhibitors contributing less than 10% (appendix p 18).

For hospitalisation for heart failure, mean follow-up time for the primary ITT analysis was 420 days for the SGLT2 inhibitor group and 427 days for the DPP-4 inhibitor group; mean follow-up time by treatment group for individual countries and overall is shown in the appendix (p 19). During 420 433 person-years of follow-up, there were 3925 outcome events; 1651 occurred in the SGLT2 inhibitor group (incidence rate 0·79 per 100 person-years) and 2274 occurred in the DPP-4 inhibitor group (1·07 per 100 person-years). The event rate by treatment group is shown in the appendix (p 20). Initiation of an SGLT2 inhibitor rather than a DPP-4 inhibitor was associated with a lower risk of hospitalisation for heart failure (ITT-unadjusted approach, pooled HR 0·69, 95% CI 0·61–0·77; p<0·0001;

	SGLT2 inhibitors	DPP-4 inhibitors	Standardised difference
Mean age, years	57·8 (SD 11·8)	57·6 (SD 12·6)	1·3%
Sex			
Women	85 169/193 124 (44·1%)	85 166/193 124 (44·1%)	0
Men	107 955/193 124 (55·9%)	107 958/193 124 (55·9%)	0
Cardiovascular disease history	56 950/186 131 (30·6%)	54 983/186 131 (29·5%)	2·3%
Myocardial infarction	8395/186 131 (4·5%)	8156/186 131 (4·4%)	0·6%
Unstable angina	9012/186 131 (4·8%)	8560/186 131 (4·6%)	1·1%
Heart failure	13 859/186 131 (7·4%)	13 333/186 131 (7·2%)	1·1%
Atrial fibrillation	8385/186 131 (4·5%)	8070/186 131 (4·3%)	0·8%
Stroke	19 661/186 131 (10·6%)	19 052/186 131 (10·2%)	1·1%
Peripheral artery disease	11 224/186 131 (6·0%)	11 057/186 131 (5·9%)	0·4%
Microvascular disease	84 427/186 131 (45·4%)	81 761/186 131 (43·9%)	2·9%
Chronic kidney disease	10 942/186 131 (5·9%)	10 636/186 131 (5·7%)	0·7%
Frailty*	15 309/180 416 (8·5%)	15 535/180 416 (8·6%)	0·4%
Other glucose-lowering drugs			
Metformin	151 250/193 124 (78·3%)	152 551/193 124 (79·0%)	1·6%
Sulfonylurea	73 058/193 124 (37·8%)	72 515/193 124 (37·5%)	0·6%
Thiazolidinedione	17 053/193 124 (8·8%)	16 416/193 124 (8·5%)	1·2%
GLP-1 receptor agonist	12 539/193 124 (6·5%)	11 129/193 124 (5·8%)	3·0%
Insulin	47 636/193 124 (24·7%)	46 292/193 124 (24·0%)	1·6%
Antihypertensive therapy	133 413/193 124 (69·1%)	131 919/193 124 (68·3%)	1·7%
Low-ceiling diuretic	26 428/193 124 (13·7%)	26 170/193 124 (13·6%)	0·4%
Angiotensin-converting enzyme inhibitor	45 798/193 124 (23·7%)	45 472/193 124 (23·5%)	0·4%
Angiotensin receptor blocker	73 969/193 124 (38·3%)	73 540/193 124 (38·1%)	0·5%
Loop diuretic	17 100/193 124 (8·9%)	16 748/193 124 (8·7%)	0·6%
Statin	121 115/193 124 (62·7%)	119 997/193 124 (62·1%)	1·2%
β blocker	49 472/193 124 (25·6%)	48 738/193 124 (25·2%)	0·9%
Aldosterone antagonist	6139/193 124 (3·2%)	6017/193 124 (3·1%)	0·4%
Index year			
2012	15/193 124 (<0·1%)	64/193 124 (<0·1%)	2·5%
2013	6682/193 124 (3·5%)	6008/193 124 (3·1%)	2·6%
2014	32 400/193 124 (16·8%)	31 528/193 124 (16·3%)	1·3%
2015	54 605/193 124 (28·3%)	54 875/193 124 (28·4%)	0·3%
2016	83 171/193 124 (43·1%)	83 204/193 124 (43·1%)	0
2017	16 251/193 124 (8·4%)	17 445/193 124 (9·0%)	3·2%

Data are n (%), unless otherwise indicated. SGLT2=sodium-glucose co-transporter-2. DPP-4=dipeptidyl peptidase-4. GLP-1=glucagon-like peptide-1. *Frailty was defined as one or more hospitalisations of 3 or more consecutive days during the year before the index date. The denominator varies for the cardiovascular history as this data was not available for Australia, and for frailty as this data was not available for Australia or Spain.

Table: **Baseline characteristics of the study population (after propensity matching)**

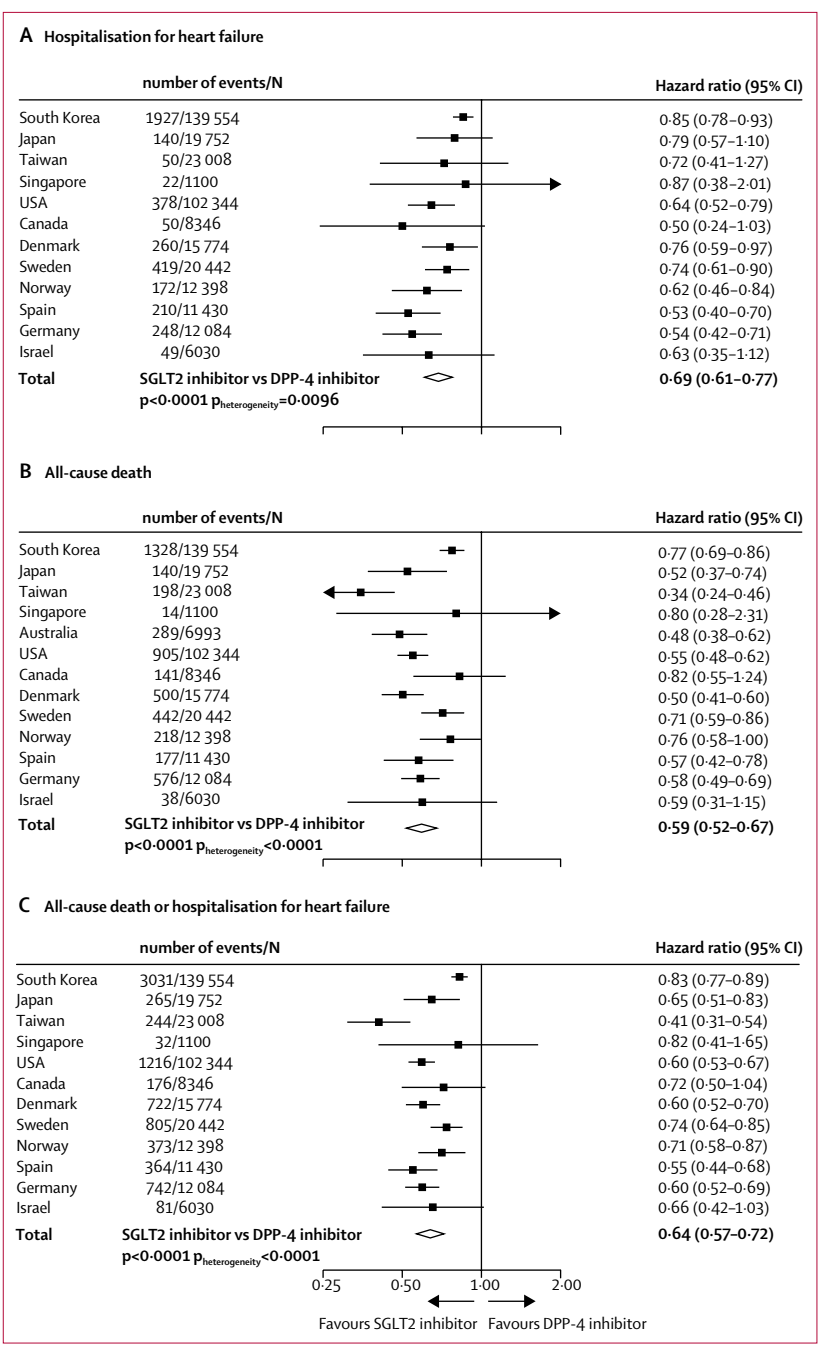
figure 2A). HRs consistently favoured SGLT2 inhibitors over DPP-4 inhibitors in each country (figure 2A). Similar results were seen in the ITT multivariate-adjusted and on-treatment analyses (appendix pp 21–22) and estimates were consistent after one country was excluded at a time in repeat analyses (appendix p 23).

For all-cause death, during 447 800 person-years of follow-up, there were 4966 deaths; 1868 occurred in the SGLT2 inhibitor group (incidence rate 0·84 per 100 person-years) and 3098 occurred in the DPP-4 inhibitor group (1·37 per 100 person-years). The event rate by treatment group is shown in the appendix (p 20). Initiation of an SGLT2 inhibitor rather than a DPP-4 inhibitor was associated with a lower risk of death (ITT unadjusted approach, pooled HR 0·59, 95% CI 0·52–0·67; p<0·0001; figure 2B). Results were directionally consistent across participating countries (figure 2B). Similar results were seen in the ITT multivariable-adjusted and on-treatment analyses (appendix pp 21–22) and estimates were consistent after one country was excluded at a time in repeat analyses (appendix p 23).

For the composite of hospitalisation for heart failure or all-cause death, during 420 433 person-years of follow-up, there were 8051 events; 3253 occurred in the SGLT2 inhibitor group (incidence rate 1·56 per 100 person-years) and 4798 in the DPP-4 inhibitor group (2·27 per 100 person-years). The event rate by treatment group is shown in the appendix (p 20). Initiation of an SGLT2 inhibitor rather than a DPP-4 inhibitor was associated with a lower risk of hospitalisation for heart failure or death (ITT-unadjusted approach, pooled HR 0·64, 95% CI 0·57–0·72; p<0·0001; figure 2C). HRs consistently favoured SGLT2 inhibitors over DPP-4 inhibitors in each country (figure 2C). Similar results were seen in the ITT multivariate-adjusted and on-treatment analyses (appendix pp 21–22) and estimates were consistent after one country was excluded at a time in repeat analyses (appendix p 23).

For myocardial infarction, during 421 232 person-years of follow-up, there were 2327 events; 1095 occurred in the SGLT2 inhibitor group (incidence rate 0·52 per 100 person-years) and 1232 occurred in the DPP-4 inhibitor group (0·58 per 100 person-years). The event rate by treatment group is shown in the appendix (p 20). Initiation of an SGLT2 inhibitor rather than a DPP-4 inhibitor was associated with a lower risk of myocardial infarction (ITT-unadjusted approach, pooled HR 0·88, 95% CI 0·80–0·98; p=0·020; figure 2D). HRs favoured SGLT2 inhibitors over DPP-4 inhibitors in most countries (figure 2D). Similar results were seen in the ITT multivariate-adjusted and on-treatment analyses (appendix pp 21–22) and estimates were consistent after one country was excluded at a time in repeat analyses (appendix p 23).

For stroke, during 420 268 person-years of follow-up, there were 3821 events; 1720 occurred in the SGLT2 inhibitor group (incidence rate 0·82 per 100 person-years) and 2101 occurred in the DPP-4 inhibitor group (0·99 per 100 person-years). The event rate by treatment group is shown in the appendix (p 20). Initiation of an SGLT2 inhibitor rather than a DPP-4 inhibitor was associated with a lower risk of stroke (ITT-unadjusted approach, pooled HR 0·85, 95% CI 0·77–0·93; p=0·0004; figure 2E). HRs favoured SGLT2 inhibitors over DPP-4 inhibitors in most countries



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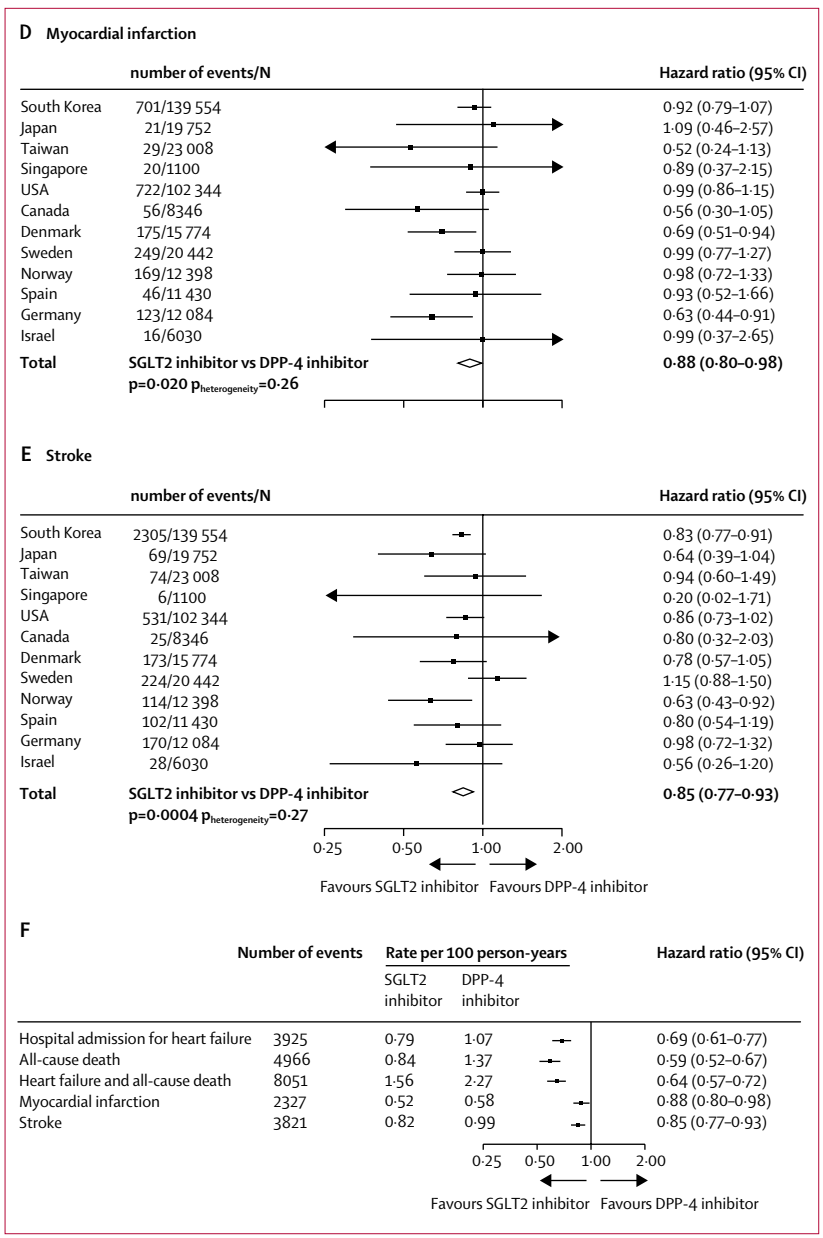

Figure 2: **Cardiovascular and mortality outcomes with SGLT inhibitors versus DPP-4 inhibitors**
Graphs show forest plots for (A) hospitalisation for heart failure, (B) all-cause death, (C) composite of all-cause death and hospitalisation for heart failure, (D) myocardial infarction, and (E) stroke, and (F) a summary of all five outcomes including rates per 100 person-years with each drug class. Data are for intention-to-treat analysis (unadjusted). SGLT2=sodium-glucose co-transporter-2. DPP-4=dipeptidyl peptidase-4.

(figure 2E). Similar results were seen in the ITT multivariate-adjusted and on-treatment analyses (appendix pp 21–22) and estimates were consistent after one country was excluded at a time in repeat analyses (appendix p 23).

A summary of the associations between initiation of SGLT2 inhibitors or DPP-4 inhibitors across the countries pooled for all outcomes is shown in figure 2F.

In the subgroup analyses, in both patients with and without cardiovascular disease at baseline, compared with initiation of a DPP-4 inhibitor, initiation of an SGLT2 inhibitor was associated with significantly lower risks of death, hospitalisation for heart failure, and death or hospitalisation for heart failure, with no significant interactions across the two subgroups. For myocardial infarction and stroke, the results were directionally consistent in favour of SGLT2 inhibitors, although HRs were non-significant for the subgroup with established cardiovascular disease at baseline, but with no significant interactions across the two subgroups (figure 3).

Discussion

In this large analysis of clinical data from 13 countries across four geographical regions, within a well-matched sample of more than 386 000 patients with type 2 diabetes, compared with initiation of a DPP-4 inhibitor, initiation of an SGLT2 inhibitor was associated with a substantially lower risk of hospitalisation for heart failure, death, and a composite outcome of death or hospitalisation for heart failure. Additionally, there was also a modestly (but significantly) lower risk of myocardial infarction and stroke in patients initiated on SGLT2 inhibitors rather than DPP-4 inhibitors. Despite variable patient characteristics, health-care settings, practice patterns, and specific SGLT2 inhibitor drugs used, the directions of associations were consistent across countries and regions and across the subgroups with or without previous cardiovascular disease.

Our present study expands on previous observational data,[14,15] using data from large populations from 13 different countries and implementing an active-comparator new-user design. The outcomes of patients with type 2 diabetes in relation to novel drug treatments, including cardiovascular events, have not been well described in regions outside of North America and Europe, despite reports of higher prevalences of cardiovascular events in these areas. We also analysed data for a substantial range of clinically relevant outcomes, including all-cause death and various cardiovascular outcomes besides hospitalisation for heart failure (eg, myocardial infarction and stroke).

The previous CVD-REAL studies showed that initiation of SGLT2 inhibitors was associated with beneficial effects on all cardiovascular outcomes assessed compared with other glucose-lowering drugs.[12,13,21,22] However, the comparator group in these studies included about 50% of patients initiated on insulin or sulfonylureas, which can cause hypoglycaemia and weight gain, and which have previously been implicated as potentially associated with increased cardiovascular risk, although randomised trials have not confirmed these risks.[23,24] By contrast, DPP-4 inhibitors and SGLT2 inhibitors are not associated with increased hypoglycaemia or weight gain, and have similar glycaemic efficacy, suggesting that the cardiovascular benefits associated with SGLT2 inhibitor initiation could be independent of their effects on blood glucose, HbA_{1c}, and bodyweight.

Our findings are in line with outcomes from large-scale randomised controlled trials. DPP-4 inhibitors have been shown to lower HbA_{1c} without beneficial short-term or mid-term effects on major adverse cardiovascular events (cardiovascular death, myocardial infarction, or stroke), hospitalisation for heart failure, or adverse renal outcomes.[8,9,25,26] Results of a meta-analysis of SGLT2 inhibitor cardiovascular outcome trials showed an overall 11% reduction in major adverse cardiovascular events (HR 0·89, 95% CI 0·83–0·96; p=0·0014).[3,27] A consistent and significant decrease in the risk of hospitalisation for heart failure has been seen in all cardiovascular outcome trials of SGLT2 inhibitors reported to date.[2] A significantly lower risk of hospitalisation for heart failure associated with initiation of SGLT2 inhibitors compared with other glucose-lowering drugs has also been previously shown in large international pharmacoepidemiological studies.[12,13,21,22] Heart failure is a highly prevalent and frequently underdiagnosed complication of type 2 diabetes and is associated with a particularly poor prognosis.[28] As no clinical trials have directly compared SGLT2 inhibitors with DPP-4 inhibitors in terms of their effect on hospitalisation for heart failure, and both classes of drug are commonly used in clinical practice, our data provide the most comprehensive assessment of this outcome to date.

Comparisons of effect sizes between observational studies and clinical trials can be challenging because of differences in the populations in which drugs are used, study design, and data ascertainment methods.[29] However, as there have been no large-scale, head-to-head comparison trials of newer oral glucose-lowering drugs to date, our study offers important information with respect to the association between the use of these drug classes and their association with cardiovascular events. The consistency of our study results across countries, irrespective of variability in health-care systems and use of specific SGLT2 inhibitors, is of particular importance, as most people with type 2 diabetes worldwide reside outside of the USA and Europe.[30] Notably, the overall incidence of both heart failure and stroke in this study were about double the incidence of myocardial infarction, and the risk of all-cause mortality was higher than the risk of having a cardiovascular event—important epidemiological observations in a large and global contemporary cohort of patients with type 2 diabetes.

This was a rigorously conducted epidemiological study, which provides important information on the relative incidence of heart failure, death, myocardial infarction, and stroke in people with type 2 diabetes. The strengths of the present study include its population-based, observational design, international scope (with use of a common data abstraction protocol and statistical analysis plan across countries), large numbers of cardiovascular events and patients from multiple countries, the longest follow-up of all observational studies of SGLT2 inhibitors to date, and a conservative methodological approach to comparative effectiveness, which was designed to avoid immortal time bias. To our knowledge, the present study is the first to address the association between initiation of SGLT2 inhibitors or DPP-4 inhibitors and cardiovascular events that covers most world regions. Two previous observational studies compared SGLT2 inhibitors with DPP-4 inhibitors. Data from Denmark, Norway, and Sweden were used to assess outcomes with the SGLT2 inhibitor dapagliflozin,[22] and data from two commercial claims and one federal claim sources in the USA were used to assess outcomes with empagliflozin.[14] However, both studies were limited by a smaller number of patients and cardiovascular events, a shorter follow-up time, and investigation of more selected cardiovascular outcomes compared with our study. Lastly, in our study, initiation of an SGLT2 inhibitor was associated with significantly lower risks of cardiovascular outcomes compared with initiation of a DPP-4 inhibitor, even in a subgroup of patients without established cardiovascular disease. The cardiovascular outcome trials for SGLT2 inhibitors to date have been done in high-risk populations; therefore, there are few data for safety or clinical benefit in patients at lower risk of cardiovascular disease events. Our results suggest that the cardiovascular benefits of SGLT2 inhibitors might be applicable to a broader patient population than previously considered. However, this finding should be interpreted with caution, as some degree of residual confounding is inherent to any observational study, and our results were not adjusted for multiple comparisons.

The results of our study should be interpreted in the context of several possible limitations. In view of the observational nature of the study, despite robust propensity matching and the use of several sensitivity analyses, the

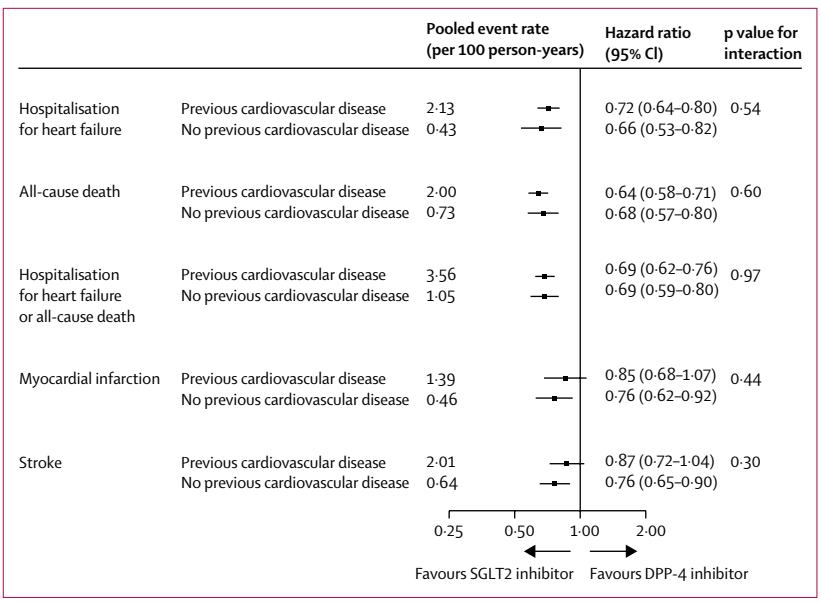

Figure 3: **Cardiovascular and mortality outcomes in patients with and without cardiovascular disease at baseline**

Data are for intention-to-treat analysis (adjusted). SGLT2=sodium-glucose co-transporter-2. DPP-4=dipeptidyl peptidase-4.

possibility of residual confounding due to unmeasured factors (malignancy, inflammatory conditions, among others) cannot be excluded. Although the propensity-matching method allows the most valid comparison of patients receiving SGLT2 inhibitors versus DPP-4 inhibitors in the context of an observational study, a sizeable proportion of patients (especially those receiving DPP-4 inhibitors) were excluded from the analysis as a result of this approach. Notably, we did not have information on lifestyle variables and had little socio-economic data for patients. However, in several countries, the costs of DPP-4 inhibitors and SGLT2 inhibitors were similar. In the large cardiovascular outcome trials of SGLT2 inhibitors (EMPA-REG OUTCOME [empagliflozin], CANVAS/CANVAS-R [canagliflozin], and DECLARE–TIMI 58 [dapagliflozin]),[2,4,5] reductions in the risks of cardiovascular events consistently occurred early in the trial (eg, at 3–6 months), and these benefits continued throughout the study (median follow-up ranged from 2·4 [CANVAS/CANVAS-R] to 4·2 years [DECLARE–TIMI 58]). Although the mean follow-up per participant in this study was 1·2 years, and the comparator was DPP-4 inhibitors and not placebo, there is no reason to suspect that the time of onset for cardiovascular benefits of SGLT2 inhibitors would be different in this context. Measures of adherence were not available in our datasets. However, our use of an ITT analysis approach is considered the most conservative, as we continued to follow-up patients and ascertain outcomes even after the medication was discontinued (use of on-treatment approach would be expected to produce more favourable results for SGLT2 inhibitors, as seen in previous studies.[12] Therefore, incorporating any measure of adherence would probably have little effect on our results. Clinical efficacy was assessed by drug class rather than by individual agent in our study. Our cohort included six different types of SGLT2 inhibitors from 13 different countries, and their use was highly variable (eg, some drugs were not available in certain regions, and different drugs dominate the markets in different countries). This substantial heterogeneity, and the fact that in some countries certain drugs were minimally used, can create highly unstable country-based statistical estimates, and present substantial challenges with clinical interpretation; thus, we felt that analyses by individual drugs in the SGLT2 inhibitor class would not be the optimal approach. A key assumption of our approach is therefore that the cardiovascular effects of DPP-4 inhibitors and SGLT2 inhibitors are homogenous across different drugs within these classes. In view of the predominance of individual SGLT2 inhibitors in some countries and regions (eg, canagliflozin in the USA and dapagliflozin in Europe), country-based analyses can also be used as surrogates for individual agents. Another limitation is that our study did not address comparative safety. Finally, for Japan and Singapore, mortality data were available only from in-hospital settings; however, most fatal events in these countries occur in hospital.[16,17]

In conclusion, in this large analysis of clinical data from 13 countries across four major geographical regions, which included more than 386 000 patients and a large number of cardiovascular events, initiation of an SGLT2 inhibitor was associated with substantially lower risks of hospitalisation for heart failure and death compared with initiation of a DPP-4 inhibitor, with consistent patterns across regions. Initiation of an SGLT2 inhibitor was also associated with modestly lower risks of myocardial infarction and stroke. These findings expand on previous evidence from large-scale clinical trials and observational studies and provide further support for the cardiovascular benefits associated with use of SGLT2 inhibitors in patients with type 2 diabetes.

Contributors

PF, MT, and MK contributed to the development of the study concept and design, data collection and analysis, data interpretation, and writing of the report. SK contributed to the data collection, data interpretation, and writing of the report. CSPL, DJK, MAC, AN, MEJ, KIB, RWH, JF-N, NT, JES, JI, AK, S-YG, C-EC, HC, EW, JB, and FS contributed to the data collection, data interpretation, and critical review and revision of the report. All authors approved the report for submission.

Declaration of interests

SK has received research grants and consulting fees from Bayer, research grants from Daiichi Sankyo, and speaker fees from Bristol-Myers Squibb and AstraZeneca. CSPL is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, and Vifor Pharma; has served as consultant or on the advisory board, steering committee, or executive committee for Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, Vifor Pharma, Novartis, Amgen, Merck, Janssen Research & Development, Menarini, Boehringer Ingelheim, Novo Nordisk, Abbott Diagnostics, Corvia, Stealth BioTherapeutics, JanaCare, Biofourmis, Darma, Applied Therapeutics, MyoKardia, Cytokinetics, WebMD Global, Radcliffe Group, and Corpus; and serves as cofounder and non-executive director of eKo.ai. DJK has received research grant support from LG Life Sciences, Chong Kun Dang, and AstraZeneca; has been a consultant for AstraZeneca, Novo Nordisk, and Sanofi; and has received speaker fees from Novo Nordisk, Takeda, Handok, CJ Healthcare, Chong Kun Dang, MSD, Hanmi, and AstraZeneca. MAC has received research grants and personal fees from Amgen, personal fees from AstraZeneca, Chiesi, Boehringer Ingelheim, Novo Nordisk, and Merck; and research grants from Bristol Myers Squibb, CSL Behring, and Novartis. AN has received honoraria for lectures and advisory board meetings from AstraZeneca, Novo Nordisk, MSD, Boehringer Ingelheim, and Lilly. MEJ has received research grants from AstraZeneca, Amgen, Boehringer Ingelheim, and Sanofi Aventis; is a shareholder of Novo Nordisk; and has received speaker fees from Novo Nordisk. KIB has received research grants and non-financial support (for keeping and maintaining the database and statistical analyses) from AstraZeneca related to the present study; and research grants from Boehringer Ingelheim, MSD, Sanofi, Novo Nordisk, and Eli Lilly. RWH has received research grants to his institution from AstraZeneca, including support for the present study. NT has received consulting fees from Boehringer Ingelheim, Eli Lilly, Otsuka, and AstraZeneca; research grants from AstraZeneca, including support for the present study; research grants from Janssen and Tricida; and consulting fees and stock options from Tricida, PulseData, and Mesentech. JES has received honoraria for advisory board participation and lectures from Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Mylan Pharmaceuticals, and Novo Nordisk. JI has consulted for AstraZeneca Australia. AK has received consulting fees from AstraZeneca, Novo Nordisk, and Boehringer Ingelheim. S-YG has received research grants to her institution from AstraZeneca, Medtronic, and Sanofi; and honoraria for advisory board participation for Amgen, AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Medtronic, and Sanofi. C-EC has received

honoraria for lectures from AstraZeneca, Boehringer Ingelheim, Daiichi-Sankyo, MSD, Novartis, Pfizer, and Sanofi. MT is an employee of Statisticon, for which AstraZeneca is a client. HC, EW, FS, and PF are AstraZeneca employees and hold stock options in the company. JB is an AstraZeneca employee. MK has received research grants from AstraZeneca and Boehringer Ingelheim; and has served as a consultant for Amarin, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Glytec, Novo Nordisk, Janssen, Merck (Diabetes), Novartis, Sanofi, and Vifor Pharma.

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